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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/211,297 | 12/14/1998 | WILLIAM J. BOYLE | A-451-F | 7253 |

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| EXAMINER |
|---|
| DEBERRY, REGINA M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 13 |

DATE MAILED: 11/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/211,297 | Applicant(s) BOYLE, WILLIAM J. | |
|---|---|---|---|
| | Examiner Regina M. DeBerry | Art Unit 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *37-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Status of Application, Amendments and/or Claims***

The amendment filed 12 September 2001(Paper No. 11) has been entered in full. Claims 37-57 are pending in the application. Newly amended claim 54 has been renumbered to 53 under Rule 126. Please see claim objections below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Withdrawn Objections And/Or Rejections***

The rejection of claims 37-57 under 35 USC 112, first paragraph as set forth at pages 3-6 of the previous Office Action (Paper No. 9 12 March 2001) is *withdrawn in part* in view of the amendment (Paper No. 11 12 September 2001).

The rejection of claims 37-57 under 35 USC 112, first paragraph, written description as set forth at pages 6-8 of the previous Office Action (Paper No. 9 12 March 2001) is *withdrawn in part* in view of the amendment (Paper No. 11 12 September 2001).

The rejection of claim 53 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention as set forth at page 8 of the previous Office Action (Paper No. 9 12 March 2001) is *withdrawn* in view of the amendment (Paper No. 11 12 September 2001). Please see claim objection below.

**Claim Objections**

Applicant did not address the claim corrections made under rule 126 set forth on page 2 in the previous Office Action (Paper No. 9 12 March 2001). Applicant states that it is assumed that the Examiner is referring to Claim 54, which recites recombinant DNA expression, and not Claim 53 (page 7, Paper No. 11 12 September 2001). This is incorrect. Under Rule 126, claim 54 was renumbered to claim 53 because Applicant inadvertently omitted a claim in a previous amendment (Paper No. 3 25 March 1999). Appropriate correction is required.

**Claim Rejections - 35 USC § 112, first paragraph**

Claims 37-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed composition wherein the recited OPGbp comprises SEQ ID NO:37 or SEQ ID NO:39, does not reasonably provide enablement for the claimed composition wherein the recited OPGbp comprises variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant's arguments (pages 3-6, Paper No. 11 12 September 2001) have been fully considered. Applicant refers to the Sullivan declaration (Paper No. 12). Applicant provides as Exhibit A; a declaration of John K. Sullivan describing anti-OPGbp antibodies which inhibit bone resorption. This declaration was submitted in connection with copending US Serial No. 09/211,315 (the 315 application) which is the same

disclosure of the present application. The Sullivan declaration under 37 CFR 1.132 filed 12 September 2001 is partly sufficient to overcome the rejection of claims 37-57 based upon 35 USC 112, first paragraph. The evidence in the Sullivan declaration is not commensurate in scope with the claimed invention. The declaration only discusses those experiments wherein antibodies were made to specific OPGbp sequences in mouse OPGbp (SEQ ID NO:37) and human OPGbp (SEQ ID NO:39) and the claims encompass antibodies made to OPGbp variants.

Applicant asserts that the various OPGbp polypeptides recited in the claims may be made without undue experimentation and naturally occurring variants of OPGbp may be readily identified by one skilled in the art using, for example, hybridization with nucleic acids in either SEQ ID NO:36 or SEQ ID NO:38 using procedures such as those described on page 9 lines 19-page 10, line 9 of the specification. Applicant asserts that the use of the various forms of OPGbp as immunogens to produce antibodies would not require undue experimentation. Applicant states that methods are provided in Example 11 for producing anti-OPGbp antibodies. Such methods are known in the art to be applicable to a variety of antigens, including those recited in the claims. Contrary to Applicants assertion, variants would require undue experimentation. Applicant does disclose various deletion fragments of OPGbp; OPGbp [158-316] (containing the minimum core TNF$\alpha$-like domain) has been immunized in animals. However, proteins comprising deletion fragments are very different from proteins comprising variants. The ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, conformation is dependent

upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick *et al.*, 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks *et al.*, 1998, Trends in Genetics 14:248-250). While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions.

Applicant states that various forms of OPGbp may be used in assays to determine antibody binding without undue experimentation. Procedures for carrying out such assays are known to one skilled in the art and are also described starting on page 48, line 28 of the specification. This is not found persuasive because the claims are drawn to compositions comprising an antibody or fragment thereof which specifically binds to an epitope of OPGbp and wherein OPGbp comprises naturally occurring variants. Modifications must first be made to the OPGbp peptide which would require undue experimentation as was discussed above. The OPGbp peptides comprising the modifications are then injected into an animal and must be tested to see that the antibody recognizes the peptide. Applicant does disclose the various assays used

when making antibodies. However as was stated above, proteins comprising deletion fragments are very different from proteins comprising variants. An antibody must be tested to ensure that an epitope is being recognized. Applicant has not disclosed which amino acid residues in OPGbp can be substituted or added while still maintaining function. OPGbp peptides comprising variant peptide could fold differently from wild type OPGbp. If the folding is effected, the specificity of binding of the antibody to its epitope could also be affected.

Claims 37-57 (as it relates to a composition comprising an antibody or fragment thereof which specifically binds to an epitope of naturally occurring variants of OPGbp ) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection was set forth on pages 6-8 of the previous Office Action (Paper No. 9 12 March 2001).

Applicant cites Vas-Cath v. Mahurkar 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). Applicant states, "possession of the invention may be shown in a number of ways, such as by actual reduction to practice, or by such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention, Lockwood v. American Airlines 41 USPQ2d 1961 (Fed. Cir. 1997)". Applicant states that the soluble forms of OPGbp and fragments thereof are described in the specification and thus Applicant had reduction to practice of the claimed soluble OPGbp polypeptides and

fragments thereof. Applicant states that naturally occurring OPG variants are described in the specification. Applicant states that, "in contrast to the facts in Fiddes and Fiers, the application provides a representative number of species within the genus of claimed OPGbp polypeptides and therefore adequately describes the invention". This is not found persuasive because the claims are drawn to compositions comprising an antibody or fragments thereof which bind epitopes of OPGbp wherein OPGbp comprises naturally occurring variants thereof. OPGbp and the deletion fragments of OPGbp are cited in the instant application. However, Applicant does not disclose naturally occurring OPGbp variants, nor does Applicant disclose the claimed invention; compositions comprising an antibody or fragments thereof which bind the epitopes of naturally occurring variants of OPGbp.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (703) 305-6915. The examiner can normally be reached on Mondays-Fridays 8:00 a.m. - 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 308-2742 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RMD

RMD
November 6, 2001

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER